# Enzymatic passaging of human embryonic stem cells alters central carbon metabolism and glycan abundance.

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**Public Summary:**
This manuscript identified metabolic consequences of stem cell cultivation procedures. As cells grow they must be split to be expanded. Some compounds used to passage or split cells cause stress by cleaving off sugars present on the outside of cells. Metabolic rates were significantly lower when using these compounds. We developed a new method of measuring the synthesis of these sugars. This approach also demonstrated an important metabolic need of stem cells in that they must regenerate glycans or sugars on the cell surface constantly.

**Scientific Abstract:**
To realize the potential of human embryonic stem cells (hESCs) in regenerative medicine and drug discovery applications, large numbers of cells that accurately recapitulate cell and tissue function must be robustly produced. Previous studies have suggested that genetic instability and epigenetic changes occur as a consequence of enzymatic passaging. However, the potential impacts of such passaging methods on the metabolism of hESCs have not been described. Using stable isotope tracing and mass spectrometry-based metabolomics, we have explored how different passaging reagents impact hESC metabolism. Enzymatic passaging caused significant decreases in glucose utilization throughout central carbon metabolism along with attenuated de novo lipogenesis. In addition, we developed and validated a method for rapidly quantifying glycan abundance and isotopic labeling in hydrolyzed biomass. Enzymatic passaging reagents significantly altered levels of glycans immediately after digestion but surprisingly glucose contribution to glycans was not affected. These results demonstrate that there is an immediate effect on hESC metabolism after enzymatic passaging in both central carbon metabolism and biosynthesis. HESCs subjected to enzymatic passaging are routinely placed in a state requiring re-synthesis of biomass components, subtly influencing their metabolic needs in a manner that may impact cell performance in regenerative medicine applications.